Did you know? Neocytolysis, how to halt EPO

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Editorial

Did you know?
Neocytolysis, how to halt EPO?

Upon demand, erythropoietin (EPO) is rapidly synthesized and released (Gunga *et al.* 1996, Wenger & Kurtz 2011). After all, there is little time to lose when reaching high altitude. Although erythropoiesis must come about promptly (Lu *et al.* 2015), you may assume that the newly formed red blood cells will circulate for the next 4 months, and it is generally accepted that erythrocyte lifespan cannot be reduced. For long-term mountain dwellers, there may be few disadvantages with long-standing increases in haematocrit. But what would happen with those who descend?

Even more challenging is to grasp how a long-standing effect (EPO-stimulated erythropoiesis) can be controlled by even more rapid stimuli than ascent. For instance, blood volume depletion swiftly stimulates EPO formation. Within minutes, elevated levels are measured following a drop in central venous pressure. Imagine standing in line during a warm day without enough to drink. EPO increases, new red blood cells are formed, and for the next 4 months, we will be experiencing an increase in haematocrit. Can this really take place?

To allow optimal erythropoiesis regulation via EPO, either a low-pass filtering effect is required, or our dogma regarding the 120-day lifespan of erythrocytes needs reconsideration. Here, insight from manned space missions comes in handy. You may have anticipated elevated EPO levels in astronauts (extreme high altitude), but the contrary is the case. Modern spaceships operate under normobaric conditions with normal oxygen concentration. Due to microgravity, volume redistribution in favour of the upper body portions takes place and the body receives a false signal of volume overload causing EPO to plunge. Men in space thus face rapid declines in the red blood cell fraction, termed 'space anemia'. Together with volume losses due to central plethora in space, these adjustments among others cause extreme orthostatic intolerance in astronauts upon landing, so that they require being lifted out of the capsule.

Given the firm erythrocyte lifespan of 120 days, space anaemia is not readily fathomed. When erythrocytes are radio-labelled well before lift-off, deeper insight into adaptation is obtained. It seems as if the old erythrocytes live on for their 120 days of life, but the newly formed red blood cells are eliminated. This phenomenon is termed as 'neocytolysis' (Alfrey *et al.* 1997). Normal EPO levels warrant continuous erythropoiesis allowing for constant haematocrit (Fig. 1). In the lack of sufficient EPO, it is the *youngest* erythrocytes disposed for disintegration by splenic reticuloendothelial cells (Fig. 1). Neocytolysis may explain why providing EPO to patients with renal failure three times weekly can fail to normalize the haematocrit. EPO half-life is only 6 hours; thus, neocytolysis is repeatedly triggered. Moreover, athletes training at high altitude must consider the best time for descent before the actual competition. Haematocrit dramatically decreases 10–14 days after return to sea level (Siebenmann *et al.* 2015), perhaps due to neocytolysis.

We still have a lot to learn on EPO-stimulated erythropoiesis, and upon the many other functions arising (Bailey *et al.* 2014, Brugniaux 2014).

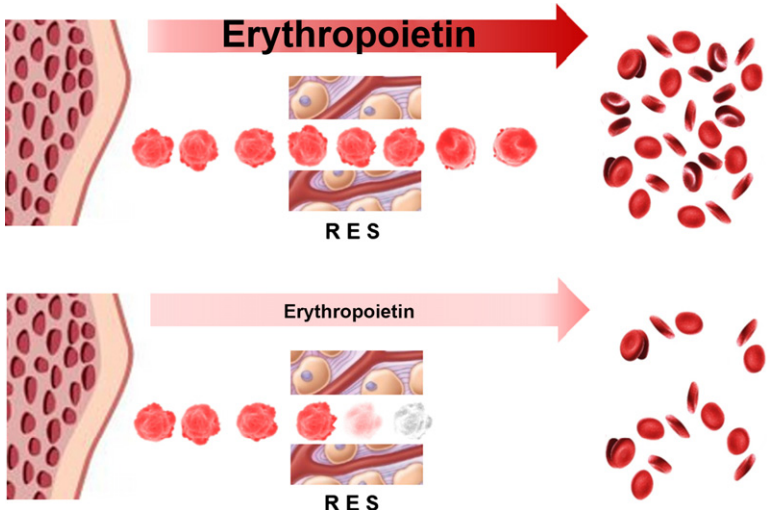

Figure 1 EPO maintains haematocrit by erythropoiesis (top). Low EPO levels lead to neocytolysis by the reticuloendothelial system (RES) and the haematocrit declines (bottom).

Conflict of Interest

None.

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